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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,490	11/05/2003	Paul S. Mischel	CST-212	7648
7590 James Gregory Cullem, Esq. Intellectual Property Counsel CELL SIGNALING TECHNOLOGY, INC. 3 Trask Lane Danvers, MA 01923			EXAMINER DUFFY, BRADLEY	
			ART UNIT 1643	PAPER NUMBER
SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE		
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Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/701,490	MISCHEL ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Brad Duffy	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 05 December 2006.  
 2a) This action is FINAL.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-24 is/are pending in the application.  
 4a) Of the above claim(s) 16-19 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-15 and 20-24 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on 05 November 2003 is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>10/07/2004</u> .  | 6) <input type="checkbox"/> Other: _____                          |

**DETAILED ACTION**

1. The examiner of the instant application has changed here at the Patent and Trademark office. Please direct future inquiries concerning this application to Brad Duffy whose telephone number is (571) 272-9935.
2. The election filed December 5, 2006, is acknowledged and has been entered. Applicant has elected the invention of Group I, claims 1-15 and 20-24. Applicant has also elected the species phospho-S6 for parts (b)-(e) of claim 1. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).
3. Claims 1-24 are pending in the application.
4. Claims 16-19 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.
5. Claims 1-15 and 20-24 are under examination.

***Information Disclosure Statement***

6. The references cited in the information disclosure statement filed on October 7, 2004, have been considered.

***Specification***

7. The disclosure is objected to because of the following informalities:
  - (a) The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code

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and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such impermissible disclosures appear in the specification at page 38, paragraph [0102].

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

(b) The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

An example of such an improperly demarcated trademark appearing in the specification is Sepharose™ (see page 33, [0087]).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

(c). The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: The specification does not appear to provide proper antecedent basis for the methods of claims 1-15. As these are original claims, the specification could be amended to provide antecedent basis without introducing new matter.

(d) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is

requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

***Claim Objections***

8. The following claims are objected to because of minor informalities:

(a) Claim 6 is objected to because claim 1 requires step (a) to be examined in addition to one or more of steps (b)-(e), but claim 6 recites that the expression of one or more of (a)-(e) is examined. Therefore, claim 6 should recite that (a) is examined and one or more of (b)-(e) are examined before reciting the agent used in examining one or more of them.

(b) Claims 7-10 are objected to as not necessarily further limiting the methods of claim 6 and claim 1. For example, claim 6 and claim 1 do not necessarily examine the presence of phosphorylated S6 ribosomal polypeptide because only one of (b)-(e) need to be examined. Therefore, it is suggested that claims 7-10 be amended to properly limit the independent claim.

(c) Claim 15 is objected to for reciting "is identified a tumor". This appears to be a typographical error and this objection would be obviated if the claim were amended to recite, "is identified as a tumor".

(d) Claim 20 is objected to for the typographical error "EFGR", because it appears that the claim should recite "EGFR".

Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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10. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1-15 are indefinite in the recitation of "likely to respond" in claims 1 and 13. While the specification indicates that a tumor "likely to respond" is a tumor likely to exhibit growth inhibition (see page 19, paragraph [0052], the term "likely" is a relative term which renders the claim indefinite. The term "likely" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree of likelihood that the tumor will respond, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Since it is unclear how "likely" the response by the tumor must be, the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

(b) Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The method steps of claim 1 only set forth a method comprising examining a mammalian glioma tumor sample for the expression of PTEN polypeptide and examining the same sample for the presence of at least one of: phosphorylated S6 ribosomal polypeptide, EGFR polypeptide, phosphorylated AKT polypeptide and phosphorylated ERK polypeptide. However, the claim also refers to correlations with potential treatments for a mammalian glioma tumor that appear to omit steps of determining either increased or decreased expression of PTEN, increased expression and/or activity of EGFR, decreased phosphorylation of S6 ribosomal polypeptide, increased phosphorylation of AKT polypeptide and/or increased phosphorylation of ERK polypeptide because the method steps in claim 1 do not actually measure these changes in expression, phosphorylation and/or activity. Claim 13 similarly monitors for the presence of phosphorylated S6 polypeptide, but appears to omit a step of determining a change in of phosphorylated S6 polypeptide. Furthermore,

claim 13 is drawn to a method for identifying a mammalian glioma tumor that does not express PTEN polypeptide, but there is no method step that relates back to this preamble. Therefore, it is unclear what steps are actually required to make these correlations and measure these changes in expression, phosphorylation and/or activity.

(c) Claims 1-15 and 20-24 are indefinite for reciting SEQ ID Nos in parentheses in claims 1, 7, 9, 13, 15, 20, 22 and 23 (e.g., see claim 1 which recites (SEQ IN NO:7), etc). As such, it is submitted that it is unclear if these references are meant to further limit the claim, or if the SEQ ID Nos are merely exemplary of polypeptides they follow. For example, if the recitation in parentheses is intended to limit the subject matter claimed, it is unclear if the polypeptide must comprise or consist of the amino acid sequence. Therefore the claim fails to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite clarity and particularity to permit the skilled artisan to know or determine infringing subject matter. Amending the claims to recite that the polypeptides comprise or consist of a particular SEQ ID NO, for example, would obviate this rejection.

(d) Claims 2 and 3 recites the limitation "is determined". There is insufficient antecedent basis for this limitation in the claim because Claim 1 does not include a step of determining phosphorylation per se, only examining a sample for the presence of the claimed phosphorylated polypeptide. Therefore it is unclear if the determination of the phosphorylation of the polypeptide would necessarily be the same as examining for the presence of the phosphorylated polypeptide.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

#### ***Claim Rejections - 35 USC § 112***

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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12. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

MPEP § 2164.01 states:

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to

satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Claims 1-12 are drawn to methods for identifying a mammalian glioma tumor that is likely to respond, or is responsive to an EGFR polypeptide (SEQ ID NO: 7) inhibitor or an mTOR polypeptide (SEQ ID NO: 2) inhibitor, the method comprising examining a sample obtained from the tumor for:

- (a) the expression of PTEN polypeptide (SEQ ID NO: 5);  
and the presence of at least one of,
  - (b) phosphorylated S6 ribosomal polypeptide (SEQ ID NO: 1);
  - (c) EGFR polypeptide (SEQ ID NO: 7)
  - (d) phosphorylated AKT polypeptide (SEQ ID NO: 4); and
  - (e) phosphorylated ERK polypeptide (SEQ ID NO: 8)

wherein decreased expression of PTEN polypeptide together with decreased phosphorylation of S6 ribosomal polypeptide in the sample, as compared to a control, identifies the glioma tumor as likely to respond or responsive to an mTOR inhibitor, and

wherein decreased expression of PTEN together with normal phosphorylation of S6 ribosomal polypeptide in the sample, as compared to a control, identifies the glioma tumor as not likely to respond or unresponsive to an mTOR inhibitor, and

wherein normal or increased expression of PTEN and increased expression and/or activity of EGFR together with increased phosphorylation of AKT and/or phosphorylation of ERK identifies the glioma tumor as not likely to respond and/or unresponsive to an EGFR inhibitor.

Claims 13-15 are drawn to methods for identifying a mammalian glioma tumor that does not express PTEN polypeptide (SEQ ID NO:5) and which is likely to respond, or is responsive to an inhibitor of mTOR polypeptide (SEQ ID NO: 2) activity, the method comprising examining a sample obtained from the tumor for the presence of

phosphorylated S6 ribosomal polypeptide (SEQ ID NO: 1) after contacting the tumor or sample with the inhibitor,

wherein an observable decrease in phosphorylated S6 ribosomal polypeptide in the sample, as compared to a control that is not contacted with the inhibitor identifies the glioma tumor as likely to respond or responsive to the inhibitor, and

wherein no observable decrease in phosphorylated S6 ribosomal polypeptide in the sample, as compared to a control identifies the glioma tumor as not likely to respond or unresponsive to the inhibitor.

The specification discloses that there is a substantial reduction in S6 phosphorylation in tumor samples from 4 out of 5 glioblastoma multiforme patients treated for 5 days with the mTOR inhibitor, rapamycin, prior to obtaining the sample, as compared to the level of phosphorylated S6 in a tumor sample obtained before treatment from the corresponding patient, and that this inhibition of S6 phosphorylation correlates with diminished tumor proliferation in these four patients (see page 41, example 8 and Figures 3A and 3B). The specification also discloses utilizing a panel of antibodies that bind to, for example, PTEN polypeptide, EGFR polypeptide, phospho-S6 ribosomal polypeptide, phospho-ERK polypeptide, and phospho-AKT polypeptides, so as to monitor the expression of these proteins and correlate their expression levels with the expression levels of either PTEN or EGFR and with Akt pathway activation and/or patient prognosis (see Table 2 on page 43 and examples 5-7 starting on page 38). However, the use of the claimed invention has not been exemplified; and moreover, there is no guidance or exemplification present in the specification that provides a predictive correlation linking *levels of expression of PTEN polypeptide, EGFR polypeptide, phospho-S6 ribosomal polypeptide, phospho-ERK polypeptide, and phospho-AKT alone or in any specific combination before, and in the absence of, treatment with any specific treatment regimen*. Therefore, the specification does not enable methods that will identify a glioma tumor as likely to respond to mTOR or EGFR polypeptide inhibitor. Furthermore, since the specification only provides guidance or exemplification that identifies a glioblastoma multiforme as responsive to a mTOR inhibitor when mTOR is shown to decrease the phospho-S6 ribosomal polypeptide

present in a tumor sample as compared to a sample from the same patient before treatment, one of skill in the art would be subject to undue experimentation to determine if any other expression pattern before treatment or change in expression pattern after treatment of these biomarkers could predictably identify a glioma as likely to respond or responsive to a mTOR polypeptide inhibitor or EGFR polypeptide inhibitor. Notably, *the specification is silent as to the PTEN status in the glioblastoma multiforme tumors of the patients* that were shown to be responsive, or not, to rapamycin treatment in Figure 3; yet, the claimed process necessarily involves an analysis of the likely responsiveness of the glioma cells to the drug (e.g., rapamycin), which depends upon a correlation between the level of one or more markers in the cells and the presence, absence, or insufficiency of PTEN. These correlations are not established by the data presented in Figure 3. Rather it is submitted that, at best, the data in Figure 3 merely show the *not unexpected finding* that following treatment with the mTOR inhibitor rapamycin, glioblastoma cells produce lower amounts of activated, phosphorylated S6 protein and have relatively decreased proliferation rates, as the prior teaches would generally be the case, since S6 acts downstream of mTOR in a signaling pathway leading to cellular proliferation. Figure 3, however, does not correlate the proliferation rate of cells treated with rapamycin, or any other inhibitor of either mTOR or EGFR, and level of S6 phosphorylation in the presence and absence or reduction of PTEN. Consequently, the amount of guidance, direction, and exemplification is not sufficient to reasonably enable the skilled artisan to practice methods commensurate with the scope of the claims because it fails to establish the correlations upon which the invention is based.

More generally, it is submitted that the disclosure is not reasonably enabling because those of skill in the art recognize that correlating biomarkers with therapeutic treatments or a patient's prognosis is highly unpredictable and that a prognostic marker is not necessarily a predictive marker of a therapeutic treatment. For example, before a cancer biomarker can be brought to successful clinical application, Tockman et al (Cancer Res, 52:2711s-2718s, 1992) teach that many highly unpredictable considerations must be validated and correlated to determine the biomarkers effectiveness (see entire document, e.g., pages 2714s and 2716s. Although the

reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman et al teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome (p. 2714s, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (p. 2716s, col 2). Furthermore, Shepard et al (J. Clin. Oncol., 24(7):1219-1220, 2006) teach that there are clear differences between prognostic biomarkers and predictive biomarkers and that each need to be evaluated independently (see entire document, e.g., page 1219, right column). Shepard et al teach that "prognostic factors are patient and tumor factors that predict patient outcome (usually survival) and are independent of treatment administered," and that "predictive factors are clinical, cellular and molecular markers that predict response of the tumor to treatment" (page 1219, right column). Therefore, it is highly unpredictable whether any of the biomarkers of the present invention have predictive value for any treatment regimen for treating any gliomas.

More particularly, there is factual evidence that the art of determining the likelihood of responsiveness of gliomas to treatment is also an unpredictable art. Mischel et al (Brain Pathol, 13:52-61, 2003, IDS filed October 7, 2004) teach, while gliomas may be highly suitable for targeted therapy using, for example, EGFR inhibitors or mTOR inhibitors, it will be critical to correlate patient sensitivity to these inhibitors with particular biomarkers, such as EGFR expression and/or PTEN loss, but nevertheless, the art teaches that correlating PTEN status to whether an mTOR inhibitor will cause growth inhibition in cancer cells is highly unpredictable. For example, Yan et al (Cancer Research, 66(4):2305-2313, 2006) teach multiple myeloma cell lines that are

sensitive to the mTOR inhibitor, rapamycin, irrespective of their PTEN status (see entire document, e.g., abstract and page 2306, right column). Furthermore, Mills et al (PNAS, 98(18):10031-10033, 2001) teach that multiple cell lines with normal PTEN are sensitive to the mTOR inhibitors, rapamycin and CCI-779 (see entire document, e.g., page 10032, third column). For example, Mills et al teach that ovarian cancer cell lines with intact PTEN, but with amplification and activation of PI3 kinase, are as sensitive to rapamycin as PTEN mutant cells (e.g., page 10032, third column). Furthermore, Mills et al teach that the cell line, DU145, which has intact PTEN, is sensitive to rapamycin, potentially because of amplification of AKT3 and downstream activation of TOR cells (e.g., page 10032, third column). Finally, Mills et al teach that even inactivation of PTEN is insufficient to predict sensitivity to mTOR inhibitors, because cells with amplified myc can be resistant to rapamycin and the cell line, MG132, which has a mutation in PTEN is resistant to rapamycin (e.g., page 10033, first column). Furthermore, Hosoi et al (Molecular Pharmacology, 54(815-824, 1998) teach two glioblastoma cell lines, SJ-G2 and SJ-G3, one of which is responsive (i.e., shows growth inhibition) when treated with rapamycin and one that is not responsive (see entire document, e.g., Table 1 and Figure 1). Notably, Hosoi teach the treatment inhibits S6 kinase (i.e., the kinase responsible for S6 ribosomal polypeptide phosphorylation, see Choe et al, Figure 2B, Cancer Res., 63:2742-2746, 2003, IDS filed October 7, 2004) in both cell lines equally (see, e.g., Figure 6A). As such, it is apparent that one cannot reliably and accurately predict whether the claimed process can be used effectively to determine the likelihood that a glioma is, or is not, responsive to any given inhibitor of mTOR or EGFR; and because the use of the claimed invention has not been exemplified, there is no factual evidence of record suggesting otherwise. Again, while the specification may provide a showing of data that establish the expected correlation between inhibition of mTOR activity and reduced levels of S6 phosphorylation, and decreased cellular proliferation, it fails to teach any relationship between any of the measured endpoints (e.g., level of phosphor-S6; proliferation rate) and PTEN status of the cells. Therefore, it is unclear if PTEN, which is upstream of S6 kinase and is upstream of mTOR (see Choe et al, Figure 2B), would be predictive of

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responsiveness to an mTOR inhibitor, because not even the activity of S6 kinase, which phosphorylates S6 ribosomal polypeptide, can predict this responsiveness in glioblastoma cells and Mills et al teach cell lines that are deficient in PTEN that are resistant to rapamycin. Therefore, since the specification does not provide any evidence or exemplification that responsiveness to either EGFR inhibitors or mTOR inhibitors correlate with any of the biomarkers claimed, one of skill in the art would be subject to undue experimentation to determine if any of the biomarkers are predictive of a glioma that is likely to respond to an EGFR inhibitor or an mTOR inhibitor. Additionally, besides the showing that reduced S6 phosphorylation after treatment with rapamycin correlates with an inhibition of glioblastoma multiforme tumor growth in 4 out of 5 patients (note, since rapamycin is well-known in the art to inhibit S6 kinase activity by inhibiting mTOR, as evidenced by Hosoi et al (supra) and others, this correlation is not unexpected), the specification provides insufficient guidance or exemplification that any other change in biomarker expression or phosphorylation level correlates with a glioblastoma multiforme tumor that exhibits reduced proliferation after treatment with an EGFR inhibitor or mTOR inhibitor. It is also noted that the PTEN status of the patients in this example is not mentioned, so it is unclear how PTEN status relates to the correlation.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

#### ***Claim Rejections - 35 USC § 102***

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-11 and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Neshat et al (PNAS, 98(18):10314-10319, August 2001, IDS filed October 7, 2004) as evidenced by Sharma et al (J. Bioscience, 11:423-433, 1987).

The claims are herein drawn to methods comprising examining samples obtained from a glioblastoma multiforme tumor for the expression of PTEN polypeptide and determining the presence of phosphorylated S6 ribosomal polypeptide subsequent to contacting the sample with an mTOR inhibitor with an antibody that binds an epitope comprising phosphorylated serine 235 in SEQ ID NO:1 (SEQ ID NO:1 is the amino acid sequence of S6 ribosomal polypeptide) and monitoring PTEN levels with a PTEN specific antibody.

Neshat et al teach that the PTEN status of the glioblastoma cell line, U87MG is null (i.e., does not express PTEN polypeptide) and contacting this cell line with the mTOR inhibitor CCI-779 and subsequently monitoring phospho-S6 in this cell line with an antibody that recognizes and binds an epitope comprising phosphorylated serine 235 in the S6 ribosomal polypeptide (see entire document, e.g., Figure 1 and 2). Neshat et al also teach monitoring PTEN by immunoblot, which inherently would require an antibody specific for PTEN (e.g., figure legend of Figure 2). Finally, as evidenced by Sharma et al the U87MG cell line was originally obtained from a glioblastoma multiforme tumor (e.g., page 424) and therefore is considered to be a sample obtained from a glioblastoma multiforme tumor.

Thus, Neshat et al anticipate these claims.

### ***Claim Rejections - 35 USC § 103***

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 1 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neshat et al (PNAS, 98(18):10314-10319, August 2001, IDS filed October 7, 2004), in view Strik et al (Cancer, 91(5):1013-1019, March 2001).

The claims are herein drawn to a methods comprising examining a paraffin embedded biopsy sample obtained from a glioma tumor for the expression of PTEN polypeptide and the presence of phosphorylated S6 ribosomal polypeptide.

Neshat et al et al teach examining glioma tumor samples for the expression of PTEN polypeptide and for the presence of phosphorylated S6 ribosomal polypeptide

and antibodies to these polypeptides (e.g., figure 2). Neshat et al do not expressly teach that tumor samples obtained from glioma tumors include paraffin embedded biopsies. This deficiency is made up for in the teachings of Strik et al.

Strik et al teach immunohistochemistry techniques to look at endostatin expression using an anti-endostatin antibody in paraffin embedded glioma tumor tissues (see entire document, e.g., page 1014, right column and 1017, right column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to examine the expression of PTEN polypeptide and the presence of phosphorylated S6 ribosomal polypeptide as taught by Neshat in paraffin embedded glioma samples as taught by Strik.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to examine the expression of PTEN polypeptide and the presence of phosphorylated S6 ribosomal polypeptide in paraffin embedded glioma samples because Neshat teach that the levels of PTEN and S6 phosphorylation are commonly altered in gliomas and the importance of monitoring PTEN and the pathways it affects (i.e phosphorylation of S6 in patients in clinical trials of mTOR inhibitors) (e.g., page 1017, right column) Therefore, since Strik et al teach that one can monitor protein levels in biopsies obtained from glioma tumors, one would be motivated to monitor PTEN levels and phosphor-S6 levels and would have had a reasonable expectation of success, in view of Neshat et al and Strik et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

18. Claims 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neshat et al (PNAS, 98(18):10314-10319, August 2001, IDS filed October 7, 2004), in view of Monia et al (US Patent 6,020,199, February 1,200).

The claims are herein drawn to kits comprising an antibody specific for PTEN polypeptide, an antibody specific for S6 ribosomal polypeptide phosphorylated at serine 235, an antibody specific for AKT polypeptide phosphorylated at serine 473, an antibody

specific for Ki-67 polypeptide and at least one secondary antibody that binds one of these antibodies.

Neshat et al teach antibodies specific for PTEN polypeptide (e.g., figure 2 legend), S6 ribosomal polypeptide phosphorylated at serine 235 (e.g., Figure 2A), AKT polypeptide phosphorylated at serine 473 (e.g., Figure 2C) and Ki-67 polypeptide (e.g., Figure 4) for use in monitoring protein levels and cell proliferation in cell lines that have been treated with a mTOR inhibitor. Rohlik et al do not expressly teach these antibodies in a kit or in the presence of secondary antibodies. This deficiency is made up for in the teachings of Monia et al.

Monia et al teach a PTEN specific antibody and secondary antibodies that would bind this antibody and kits comprising these antibodies for detecting the level of PTEN in a sample. (see entire document, e.g., columns 12, 37 and 44).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to make kit comprising an antibody specific for PTEN polypeptide, an antibody specific for S6 ribosomal polypeptide phosphorylated at serine 235, an antibody specific for AKT polypeptide phosphorylated at serine 473, an antibody specific for Ki-67 polypeptide and at least one secondary antibody that binds one of these antibodies to monitor protein expression levels in cell lines treated with mTOR inhibitor as taught by Neshat.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to make such a kit because Neshat et al teach that these proteins are commonly monitored after treating a cell line with mTOR inhibitor and Monia et al teach that PTEN antibodies are commonly included in kits with secondary antibodies. Thus, there would be an advantage and a reasonable expectation of success in making a kit comprising an antibody specific for PTEN polypeptide, an antibody specific for S6 ribosomal polypeptide phosphorylated at serine 235, an antibody specific for AKT polypeptide phosphorylated at serine 473, an antibody specific for Ki-67 polypeptide and at least one secondary antibody as these antibodies were commonly available and antibodies are commonly put in kits, in view of Neshat et al and Monia et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

***Conclusion***

19. No claims are allowed.
20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,  
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PRIMARY EXAMINER